PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PH02109 PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/05577	International filing date *(day/month/year)* 19.12.2003	Priority date *(day/month/year)* 20.12.2002
International Patent Classification (IPC) or both national classification and IPC A61K51/04		
Applicant HAMMERSMITH IMANET LIMITED et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18.06.2004	14.04.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Gonzalez Ramon, N Telephone No. +31 70 340-3466

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/05577

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-16 as originally filed

Claims, Numbers

1-11 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-11 in part

   because:

   ☒ the said international application, or the said claims Nos. 11 in relation to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-11 in part

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-11
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	11

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 11 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

The applicant's attention is drawn to the fact that claims or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

In the present application, the International Searching Authority has restricted the search under the following objections under Articles 5 and 6 PCT:

Claims 1-8 encompass a genus of compounds defined only by their function "solid support" (claims 1-3, 6-8); "a linker" (claims 1-4, 6-8); "a protecting group" (claims 1-6, 8) wherein the relationship between the structural features of the members of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition.

The fact that one could have assayed a compound of interest using the described assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.

Therefore, claims 1-8 do not fulfil the requirements of Art. 5 and Art. 6 PCT

Moreover claims 1-4, 6-8 cover all compounds having these characteristics or properties: "solid support" (claims 1-3, 6-8); "an anion" (claims 1-4, 6-8); "a linker" (claims 1-4, 6-8); "a protecting group" (claims 1-6, 8); "an amino protected derivative" (claims 1-4, 6-8); "haloalkyl" "alkoxy", "hydroxyalkyl" (claim 4), whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds.

Support is only to be found in the present application for those parts relating to the compounds explicitly **disclosed by chemical name in claims 2, 4, 7** excluding the vague terms "protecting group", "amino protected derivative" and in the examples and to those linkers mentioned in the description at pages 4, 5 and protecting groups at page 7, line 18-21.

Furthermore present claims 1, 3, 4, 6, 8-11 do not comply with Art 5 PCT:

No support is to be found in the present application for a process for the production of an 18F labelled tracer encompassed under formula IIb which comprises treatment of a solid support-bound precursor of formula Ib or a precursor IIIb with a source of 18F to produce the labelled tracer.

An enumeration of said precursors is disclosed (page 6, 7) but no process for the production of the same is effectively disclosed.
A mere speculative statement "this chemistry may be used by analogy to prepare amine protected uracil or cytosine iodonium salt derivatives for use in radiofluorination reactions as described above" (page 16 lines 15-17) is not to be considered as sufficient support and disclosure for the skilled man in order to perform the invention (Art 5 PCT).

The only effective disclosure refers to process of production of 18F labelled compounds of formula IIa from precursors Ia and IIIa.

No international Preliminary Examination will be carried out in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT).

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or

industrial applicability; citations and explanations supporting such statement

For the assessment of the present claims 11 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The following documents (D) are referred to in this communication:

D1: Bioorganic & Medicinal Chemistry Letters (2000), 10(14), 1501-1503
D2: Applied Radiation And Isotopes, Pergamon Press Ltd., Exeter, Gb (09-2002), 57(3), 347-352
D3: Nuclear Medicine Communications (1985), 6, 455-459
D4: European Journal Of Nuclear Medicine (1989), 15(5), 225-9 (0000), , -
D5: International Journal Of Peptide And Protein Research (1991), 37(5), 430-439
D6: WO-A-9742203
D7: US-A-5312592

Novelty (Art 33(2) PCT).

The subject-matter of claims 1-11 appears to be new in the sense of Article 33(2) PCT.

Inventive step (Art 33 (3) PCT)

The subject-matter of claims 1-11 as far as novel does not involve an inventive step in the sense of Article 33(3) PCT.

The problem to be solved by the present application is the improvement in synthetic methods for introducing 18F, in particular to obtain 18F labelled tracers for PET rapidly and with good radiochemical yield (see page 1, lines 10-15)

As solution to this problem a process comprising treatment of a solid support-bound

precursor of general formula I with 18F to produce the labelled tracer of formula II as depicted in claim 1 (in particular fluorouracil and fluorocytosine) as well as the compound of formula I per se are proposed. A pharmaceutical kit and cartridge for the preparation of said 18F labelled tracer of general formula II and the use of the kit or cartridge in positron emission tomography (PET) are also encompassed.

The skilled man, aware that 18F has been incorporated into biological molecules including peptides proteins and nucleotides or into aminoacids, carbohydrates, purines, pyrimidines, steroids by processes comprising the treatment of the corresponding **solid support-bound precursor with a source of 18F to produce the labelled tracer,** would not have applied the particular claimed use of trifluoromethylsulphonate (triflate) as "Y anion" in 18F labelling process in order to render the 18F labelled compounds for PET **encompassed by present formulas II, IIa, IIb.**

However, the attention of the applicant is drawn to the fact that all embodiments covered by the claims should satisfy the criteria of inventive step. When the inventive step is solely based on the achievement of a technical effect, such as "process for the production of an 18F labelled tracer" in the present case, substantially all embodiments of independent claim 1 should exhibit this effect.

It is evident that the number of compounds encompassed by chemical groups defined as "solid support" (claims 1-3, 6-8); "a linker" (claims 1-4, 6-8); "a protecting group" (claims 1-6) is such that it is unlikely that all of them posses the effect claimed.

Therefore, as part of the subject matter of claims 1-8 does not exhibit this particular technical effect in a credible manner, said subject matter cannot involve inventive step.

Moreover the particular features of present claims 9, 10 cannot either be considered as providing an inventive step to the subject matter of the present application, as kits for the preparation of radiopharmaceuticals including a de-ionizing column (see D7, claim 3) as well as a cartridge for solid phase deprotection of the resultant product (see D6, claims 1, 24) have been described.